

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Date of mailing (day month year)
24 August 2000 (24.08.00)

To:
Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

International application No.
PCT/GB00/00090

Applicant's or agent's file reference
REP05909WO

International filing date (day month year)
14 January 2000 (14.01.00)

Priority date (day/month/year)
15 January 1999 (15.01.99)

Applicant

CHOW, Sek., Chuen et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

02 August 2000 (02.08.00)



in a notice effecting later election filed with the International Bureau on:

2. The election was was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Pascal Piriou

Facsimile No.: (41-22) 746-1436

Telephone No.: (41-22) 338 83.38

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|---|--|
| Applicant's or agent's file reference REP05909W0 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/GB 00/ 00090 | International filing date (day/month/year) 14/01/2000 | (Earliest) Priority Date (day/month/year) 15/01/1999 |
| Applicant UNIVERSITY OF NOTTINGHAM et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/00090

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K35/56 A61P29/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | WO 95 12615 A (UNIV NOTTINGHAM ; PRITCHARD DAVID IDRIS (GB)) 11 May 1995 (1995-05-11) * see in particular page 4, and claims 1,2,4-9 * | 1-3 |
| Y | --- | 4,5 |
| X | BROPHY ET AL.: "Glutathione S-transferase (GST) expression in the human hookworm <i>Necator americanus</i> : potential roles for excretory-secretory forms of GST" ACTA TROPICA, vol. 59, 1995, page 259-263 XP000881639 * see in particular pages 259-260, 262 * | 1-3 |
| Y | --- | 5 |
| | -/- | |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex

Special categories of cited documents:

- A" document defining the general state of the art which is not considered to be of particular relevance
- E" earlier document but published on or after the international filing date
- L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- O" document referring to an oral disclosure, use, exhibition or other means
- P" document published prior to the international filing date but later than the priority date claimed

- T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- > document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- &" document member of the same patent family

Date of the actual completion of the international search

28 April 2000

Date of mailing of the international search report

09/05/2000

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

Iserit, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/00090

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| Y | <p>KALINKOVICZH ET AL.: "Decreased CD4 and increased CD8 counts with T-Cell activation is associated with chronic helminth infection" CLIN. EXP. IMMUNOLOGY, vol. 114, no. 3, December 1998 (1998-12), pages 414-421, XP000881640 *see in particular the abstract, page 415 (1st paragraph), Figure 2 and sentence bridging the columns at p. 417 *</p> <p>---</p> | 4 |
| Y | <p>BEHNKE ET AL.: "Resistance of the hookworms <i>Ancylostoma ceylanicum</i> and <i>Necator americanus</i> to intestinal inflammatory responses induced by heterologous infection" INT. J. PARASITOLOGY, vol. 24, no. 1, 1994, pages 91-101, XP000881612 * see in particular the abstract & Discussion *</p> <p>-----</p> | 5 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/00090

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|-------------------------|------------------|
| WO 9512615 | A 11-05-1995 | NONE | |

PATENT COOPERATION TREATY

PCT

REC'D 12 MAR 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

| | | |
|---|--|---|
| Applicant's or agent's file reference REP05909WO | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/GB00/00090 | International filing date (day/month/year) 14/01/2000 | Priority date (day/month/year) 15/01/1999 |
| International Patent Classification (IPC) or national classification and IPC A61K35/56 | | |
| Applicant UNIVERSITY OF NOTTINGHAM et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 02/08/2000 | Date of completion of this report 08.03.2001 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Isert, B Telephone No. +49 89 2399 8691 |



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00090

I. Basis of the report

1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):

Description, pages:

1-5 as originally filed

Claims, No.:

1-5 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/00090

the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)): *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 4,5
 No: Claims 1-3

Inventive step (IS) Yes: Claims 4
 No: Claims 5

Industrial applicability (IA) Yes: Claims 1-5
 No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/00090

SECTION V:

1). The following documents (D) cited in the International search report are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 = WO-A-95 12615

D2 = Acta Tropica, 1995, 59(3): 259-263

D3 = Clin. Exp. Immunol., 1998, 114: 414-421

D4 = Int. J. Parasitology, 1994, 24(1): 91-101

Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

2). Novelty:

The subject-matter of claims 1-3 is not novel over D1 and D2, which describe compositions comprising "Excretory-secretory" (ES) products from hookworm *Necator americanus* having an effect in medicine.

The present ES products being "capable of inducing apoptosis..." have been obtained by a particular process (c.f. description pages 3-4). The processes used in D1 and D2 to obtain the ES products are fairly similar thereto. Therefore it appears justified to assume that the ES products of D1 and D2 would also be capable of inducing apoptosis.

3). Inventive step

3.2 The subject-matter of claim 4 is considered inventive:

The present application further relates to the treatment of cancer. It has been shown that the excretory-secretory (ES) products from hookworm *Necator americanus* have

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/00090

pro-apoptotic effects in vitro.

D3 shows enhanced apoptosis in Africans newly infected with helminths (inter alia Necator am.). The problem to be solved could be to identify the active principle producing said effect. However, there is no particular hint pointing to Necator americanus as the origin of the pro-apoptotic effect.

3.2 The subject-matter of claim 5 is not considered inventive:

D1 describes medical uses of "Excretory-secretory" (ES) products from hookworm Necator americanus, that are considered to be capable of apoptosis induction, see section 2 above. Thus on the basis of D1 the problem could be to identify further therapeutic uses of the ES products.

In the present application it has not been shown that the ES products actually have anti-inflammatory effects, thus solve the problem posed. Moreover, said effect is considered obvious from D2 and D4 which show and/or suggest that anti-inflammatory products are produced by Necator americanus subsequently to an infection.

4. Industrial applicability

The pharmaceutical products and uses according to claims 1-5 are considered industrially applicable under Article 33 (4) PCT.

SECTION VII

5). Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII

6). The excretory-secretory product according to claim 1 should be defined by

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/00090

appropriate product-by process claims. It is unclear, eg., whether the product comprises the mere supernatant or fractionated preparations thereof. The terms "substantially pure" and "functional fragment" used in claim 1 seem to lack appropriate definition.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|--|---|
| (51) International Patent Classification 7 : A61K 35/56, A61P 29/00, 35/00 | | A1 | (11) International Publication Number: WO 00/41706 |
| | | | (43) International Publication Date: 20 July 2000 (20.07.00) |
| <p>(21) International Application Number: PCT/GB00/00090</p> <p>(22) International Filing Date: 14 January 2000 (14.01.00)</p> <p>(30) Priority Data: 9900930.0 15 January 1999 (15.01.99) GB</p> <p>(71) Applicant (for all designated States except US): UNIVERSITY OF NOTTINGHAM [GB/GB]; University Park, Nottingham NG7 2RD (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): CHOW, Sek, Chuen [MY/GB]; University of Nottingham, University Park, Nottingham NG7 2RD (GB). PRITCHARD, David, Idris [GB/GB]; University of Nottingham, University Park, Nottingham NG7 2RD (GB).</p> <p>(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).</p> | | <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p> | |
| <p>(54) Title: PRO-APOPTOTIC AGENTS</p> <p>(57) Abstract</p> <p>A substantially pure excretory-secretory product is isolatable from <i>Necator americanus</i> and is capable of inducing apoptosis in reactive T cells.</p> | | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/00090

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/56 A61P29/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | WO 95 12615 A (UNIV NOTTINGHAM ; PRITCHARD DAVID IDRIS (GB)) 11 May 1995 (1995-05-11) * see in particular page 4, and claims 1,2,4-9 * | 1-3 |
| Y | --- | 4,5 |
| X | BROPHY ET AL.: "Glutathione S-transferase (GST) expression in the human hookworm <i>Necator americanus</i> : potential roles for excretory-secretory forms of GST" ACTA TROPICA, vol. 59, 1995, page 259-263 XP000881639 * see in particular pages 259-260, 262 * | 1-3 |
| Y | --- | 5 |
| | -/- | |



Further documents are listed in the continuation of box C



Patent family members are listed in annex.

Special categories of cited documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"8" document member of the same patent family

Date of the actual completion of the international search

28 April 2000

Date of mailing of the international search report

09/05/2000

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Fax: (+31-70) 340-3016

Authorized officer

Isert, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/00090

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| Y | <p>KALINKOVICZH ET AL.: "Decreased CD4 and increased CD8 counts with T-Cell activation is associated with chronic helminth infection" <i>CLIN. EXP. IMMUNOLOGY</i>, vol. 114, no. 3, December 1998 (1998-12), pages 414-421, XP000881640 *see in particular the abstract, page 415 (1st paragraph), Figure 2 and sentence bridging the columns at p. 417 *</p> <p>-----</p> | 4 |
| Y | <p>BEHNKE ET AL.: "Resistance of the hookworms <i>Ancylostoma ceylanicum</i> and <i>Necator americanus</i> to intestinal inflammatory responses induced by heterologous infection" <i>INT. J. PARASITOLOGY</i>, vol. 24, no. 1, 1994, pages 91-101, XP000881612 * see in particular the abstract & Discussion *</p> <p>-----</p> | 5 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/00090

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|-------------------------|------------------|
| WO 9512615 | A 11-05-1995 | NONE | |